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TOWNSEND and TOWNSEND and CREW LLP

By: _____

Lata Olivier

PATENT
Attorney Docket No. 015280-356100US
Client Ref. No. E-201-1998/0-US-06

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No. 3958
PASTAN et al.	Examiner: Zeman, Robert A.
Application No.: 09/673,707	Technology Center/Art Unit: 1645
Filed: January 11, 2001	APPELLANTS' REPLY BRIEF UNDER 37 C.F.R. § 41.41
For: RECOMBINANT IMMUNOTOXIN DIRECTED AGAINST THE HIV-1 GP120 ENVELOPE GLYCOPROTEIN	

Mail Stop Appeal Brief
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Pursuant to 37 C.F.R. §41.41, Appellants hereby submit their Reply Brief in response to the Examiner's Answer mailed on July 9, 2008, regarding the above-referenced application.

As will be seen below, the Examiner's Answer is erroneously states that the Appellants did not contest one of the grounds of rejection. The Appeal Brief, however, not only sets forth the ground of rejection but also contains Appellants' substantive argument refuting the ground. Further, the Examiner's Answer attempts to rebut the Appellants' contentions with an unsupported argument never before raised during the more than five years of prosecution of this application, and at a point when the Appellants are prohibited by rule from introducing evidence in response. The Board should reject the Examiner's attempt to introduce arguments for the first time in the Answer. Finally, the Answer tries to discredit the evidence submitted by the Appellants based on unsupported innuendo. The Answer's position is not, however, supported

by evidence of record. The Board should consider the evidence of record and, on the basis of that evidence, reverse the rejections against the claims.

ARGUMENT

1. The Answer's Assertion That the Rejection Under §112, Second Paragraph Is Not Under Review Is A Straightforward Error.

At page 3, item 6, the Examiner's Answer states that the rejection of claims 1, 52, 68, and 74 under 35 U.S.C. § 112, second paragraph, are "not under review because they have not been presented for review in the appellant's brief."

Contrary to the Answer's assertion, the rejection under §112, second paragraph is specifically set forth in the Appellants' Appeal Brief at page 4, section 6 B as a ground of rejection to be reviewed. The substantive argument rebutting the ground of rejection is set forth in the Appeal Brief at section 7 III, beginning at the bottom of page 25 and continuing until page 27. Accordingly, the Answer's position is without merit.

As the Appeal Brief clearly contests this ground of rejection, the Board is respectfully requested to dismiss the Answer's erroneous contention that it does not, and, in turn, to dismiss the unequally erroneous rejection that the claims are indefinite.

2. The Answer's Response To The Appeal Brief Introduces A New Argument. Like the Previous Arguments, The New One Relies On Speculation Rather than Fact And Should Be Dismissed.

A. Introduction

The Final Action rejects the claims as obvious under 35 U.S.C. § 103(a) over Matsushita et al., Aids Research Human Retroviruses 6(2):193-203 (1990) (hereafter, "Matsushita"), in view of Barbas, Proc Natl Acad Sci (USA) 91:3809-3813 (1994) (hereafter "Barbas") and Pastan, U.S. Patent No. 5,458,878 (hereafter, "the '878 Patent"). The Matsushita reference discloses an antibody, named "0.5β", which binds to an HIV-1 glycoprotein known as gp120. The 0.5β antibody binds to a portion of gp120 that mutates rapidly and is variable among

strains of HIV. In the Matsushita reference, the antibody was coupled to a mutated *Pseudomonas* exotoxin A (hereafter, "PE"). Since 2003, the Examiner has taken the position that, given that Matsushita disclosed an antibody reactive with a number of HIV isolates, it would have been obvious for one of ordinary skill to use the 3B3 antibody in place of the 0.5β antibody in the Matsushita immunotoxin. *See, e.g.,* June 9, 2003 Office Action at pages 10-11.

Applicants rebutted the rejection by introducing evidence that, after the Matsushita reference was published, immunoconjugates of CD4, which also binds to gp120, and PE, went into clinical trial, and failed.[1] Until the Final Action, the Examiner simply dismissed the evidence regarding the CD4-PE conjugates by asserting that they were not analogous to the immunotoxins of the invention.[2] As noted in Appellants' Appeal Brief, when the Examiner finally articulated the rationale for his position, it turned out to be based on the belief that CD4-PE would "target any cell expressing CD4", while the Matsushita immunotoxin would bind only to cells infected with HIV. Applicants corrected this fundamental misunderstanding with the declaration of Dr. David FitzGerald (the "Declaration"), a non-inventor who is an expert in the area of targeted toxins such as immunotoxins and who was a co-author on seven pre-clinical studies on CD4-PE. The Declaration explained that CD4-PE does not bind to CD4-expressing cells and that CD4-PE and the Matsushita immunotoxin were in fact analogous in terms of the cells that they were intended to bind.

The Final Action acknowledged the factual errors which underlay the rejection for the previous three years, but recharacterized the grounds of the rejection in a way that continued asserting that the CD4-PE conjugates and the claimed immunotoxins are not analogous. Using that recharacterization, the Final Action concluded that the CD4-PE 1994 clinical trial results are

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[1] The immunoconjugate discussed in the Ramachandran reference is CD4-PE, while that of Davey is soluble CD4 ("sCD4")-PE. Since the difference between the two immunoconjugates is irrelevant for purposes of the present discussion, for ease of reference they will be referred to collectively as "CD4-PE" in this Reply Brief.

[2] Since CD4 is a cell surface determinant, not an antibody, chimeric molecules comprising CD4 and a toxin are not generally referred to in the art as "immunoconjugates" or "immunotoxins." The Examiner, however, referred to the CD4 conjugates as "immunotoxins" throughout the prosecution, and Dr. FitzGerald referred to them as such in his Declaration to avoid confusion as he quoted portions of the April 13, 2006 Office Action and then responded to the quoted passages. Accordingly, the discussion below will generally refer to chimeric molecules comprising CD4 and a toxin, such as PE, as immunotoxins when summarizing the Examiner's contentions and in presenting Dr. FitzGerald's Declaration, and will otherwise refer to them as "conjugates."

less relevant than the *in vitro* results reported in the 1990 Matsushita reference. According to the Final Action:

> "the rejection was maintained based on the fact that Matsushita's immunotoxin was shown to have efficacy. Since Matsushita's immunotoxin [] comprises the same components (i.e., a PE toxin and an anti-gp120 antibody) its demonstrated efficacy would have a greater impact on the skilled artisan than the failure of a[n] immunotoxin comprising differing components (i.e., a PE toxin and CD4)."

Final Action, at page 5.

Thus, the Final Action's rejection of the CD4-PE immunoconjugates as analogous to the immunotoxins of the invention was not they do not bind to the same cells, as previously, and incorrectly, asserted, but that they were not comprised of the "same components." Since both the Matsushita antibody and CD4 both bind gp120, however, the Action's rejection failed again to explain why a person of skill would expect a different result using an anti-gp120 antibody rather than CD4.

In the Examiner's Answer, the Examiner has now again switched the basis of the rejection, but retained the rejection. He has abandoned his previous theory that CD4-PE immunotoxins would bind all cells that express CD4 and his previous theory that they do not share the "same components" as those of Matsushita. Instead, he has again recharacterized the grounds of rejection to provide a new reason that the CD4-PE conjugates and the claimed immunotoxins are allegedly not analogous. Unfortunately, the Examiner's new rationale is unsupported and completely speculative. Moreover, it has been introduced at a point in the proceedings during which the Appellants are prohibited from introducing evidence to refute the new rationale. See, 37 C.F.R. § 41.41(a)(2). Appellants respectfully request that the Board strike this unsupported and untimely argument.

B. The Answer's Arguments and Appellants' Replies Thereto

(i) Contention That The Alleged Motivation Created by The Matsushita Reference Was Not Destroyed by the CD4-PE Clinical Trials

1. Argument That CD4-PE Would Bind To The Natural Ligands Of CD4

As shown in the preceding section, Appellants presented evidence that the Matsushita immunotoxins and the CD4-PE immunoconjugates are analogous and that the results of the CD4-PE clinical trials discouraged practitioners from further development of anti-Env toxins, including anti-gp120 immunotoxins. The Examiner contended, first, that the two immunotoxins were not analogous because the CD4-PE immunoconjugates would bind to any cell expressing CD4 while the Matsushita immunotoxins would only bind to cells expressing the HIV glycoprotein gp120. When that position was shown to be factually incorrect, the Examiner then contended in the Final Action that the CD4-PE immunotoxins did not share the "same components" as those of Matsushita. Finally, the Examiner also contended that there was "some cellular or endocrine cascade present in man but not in the mouse" that was responsible for the hepatotoxicity seen in the CD4-PE clinical trials.

As observed in the Appellants' Appeal Brief, in the April 13, 2006 Office Action, the Examiner contended that:

> "since the CD4-PE immunotoxin would bind to any cell expressing CD4 on its surface, the hepato[to]xicity would logically be the result of said immunotoxin binding to healthy cells thereby disrupting some cellular or endocrine cascade present in man but not the mouse."

April 13, 2006 Action, at pages 6-7, bridging paragraph (emphasis added). Thus, the April 2006 Action expressly attributed the hepatotoxicity of the CD4-PE immunoconjugates to the alleged tendency of CD4 to bind to healthy CD4-expressing cells. In turn, the alleged tendency to bind healthy cells was cited as support for the Action's conclusion that the CD4-PE immunoconjugates were not analogous to the immunotoxins of the invention, which the Action considered not to have that tendency. See, Appeal Brief, at page 17. The Appellants observed that the basis of this contention had been refuted by the FitzGerald Declaration, *id.*, and that the

assertion that the hepatotoxicity of the CD4-PE conjugates was due to an alleged "cellular or endocrine cascade present in man but not in the mouse" was unsupported speculation cloaked in scientific-sounding language. See, Appeal Brief, at page 18.

The Answer now tries to patch the hole in the previous theories as to why the Matsushita immunotoxins and the CD4-PE immunoconjugates are allegedly not analogous. According to the Answer, the Appellants' arguments ignore the fact that CD4-PE immunotoxins would "bind to all the natural ligands of CD4 (IL16 etc.) thereby affecting untold cellular processes and endocrine cascades." Answer, at page 6.[3] The Answer states that anti-gp120-PE immunotoxins would, in contrast, bind only to cells expressing gp120, that is, cells infected with HIV-1, and concludes that the gp120-PE and the CD4-PE immunotoxins are not equivalent. *Id.* The Answer then takes the assertion that the CD4-PE immunotoxins would affect untold cellular processes, and further asserts that this is the reason for the failure of the CD4-PE immunotoxins in clinical trials. Answer, at page 12.

So far as Appellant can determine, the assertion that CD4-PE binds to natural ligands "thereby affecting untold cellular processes and endocrine cascades" is an argument new to the Answer, it is not one ever made during the more than five years of prosecution of the subject application. More importantly, it is once again unsupported speculation cloaked in scientific-sounding language. No evidence of record or presented with the Answer indicates that any "cellular processes and endocrine cascades" related to CD4-PE exist. The rationale is therefore merely an invitation to the Board to share the Examiner's speculation that they might.

The Answer then compounds this unsupported speculation with the further new speculation that these newly-hypothesized "untold cellular processes and endocrine cascades" were the reason the CD4-PE immunoconjugates failed in clinical trials. Answer, at page 12. Once again, however, the Answer presents no evidence to support its new hypothesis.

Further, having introduced a new argument not previously before raised, the Answer then states it is a fact of record. Answer, at page 13, first bullet point. As discussed

above, however, this is not only not a fact of record but it is in fact a new rationale presented for the first time in the Answer. The Answer then contends that this "fact of record" shows that the CD4-PE and Matsushita immunotoxins therefore have "radically different binding specificities". *Id.*, at second bullet point. To the contrary, however, both immunotoxins will bind to HIV-infected cells expressing gp120. The Answer then states that the Appellants have ignored the fact that CD4-PE immunotoxins would bind to targets other than HIV infected cells. Answer, at page 14, first bullet point. The Answer is correct that Appellants did not address this rationale, since it was not previously presented. The reader will note, however, that the Answer carefully states that "CD4-PE immunotoxins would bind to *targets* other than HIV infected cells" (emphasis added). This is presumably because the Answer cannot point to any cell bound by CD4. The only "target" of CD4-PE other than an HIV infected cell that the Answer can identify is IL-16. IL-16 is an interleukin, which by definition is a secreted protein. It would therefore be free in the circulation, not bound to a cell or tissue. There is therefore no evidence that CD4-PE would bind to any cell other than one infected by HIV-1 and expressing gp120. While the Answer invites the reader to draw conclusions from the possible binding of CD4-PE to IL-16, it presents no support as to its effects.

In other words, after five years of prosecution, the Answer introduces a new rationale for the obviousness rejection. Without providing any evidence, the Answer not only asserts that this new rationale is the reason persons of skill would not consider the two immunotoxins analogous, but compounds this speculation with a further, and again unsupported, speculation that this new rationale was the reason the first immunotoxin failed in clinical trial. The Board should recognize the Answer's argument for the unsupported speculation it is, and dismiss it.

While the above observations are themselves reason to dismiss the Answer's new rationale, Appellants respectfully note that, to the extent there is evidence of record, it contradicts the Answer's newly-discovered rationale. As Dr. FitzGerald states in his Declaration,

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[3] The Answer restates its points several times. The argument that CD4 will bind its "natural ligands" is also stated at, e.g., pages 9, 10, 12 and 13. The discussion above is intended to address each of the instances of this

CD4 interacts with Major Histocompatibility Complex ("MHC") class 2 molecules, which are primarily found on macrophages and other antigen presenting cells. See, FitzGerald Declaration, Appellants' Evidence Appendix, Exhibit E, at ¶16. Dr. FitzGerald notes that there "was some intellectual concern that CD4-PE toxins would bind to macrophages and other cells that express MHC class 2 molecules. This concern was tested pre-clinically, and found not to be a concern." (More specifically, the interaction of CD4-PE and cells bearing MHC class II molecules was found "not [to] interfere with cellular responses known to be dependent on functional association between CD4 and MHC Class II molecules." *See*, abstract, Berger et al., AIDS Res Human Retroviruses 6(6):795-804 (1990), Appellants' Evidence Appendix II, Exhibit E3.)

Further, as set forth in the specification, at pages 35-36, bridging paragraph, pre-clinical studies on CD4-PE showed that it was "very well tolerated by monkeys" which could have relatively high doses "administered daily for 10 days without serious toxicity." This was another reason the very high toxicity seen in the human clinical trials was such a surprise. *Id.* Thus, the "untold cellular processes and endocrine cascades" hypothesized by the Answer were not seen either in human cells in the *in vitro* tests referenced by Dr. FitzGerald, or in *in vivo* studies in animals. Thus, the processes and cascades hypothesized by the Answer would have to exist in man - but not in human cells that express MHC class II molecules - or in non-human primates. Once again, however, the Answer fails to set forth any evidence that such processes or cascades exists.

The Answer does identify a natural ligand for CD4: interleukin (IL)-16. But the Answer provides no evidence that there is any connection between the binding of CD4 to IL-16 and the hepatotoxicity seen in the CD4-PE clinical trials. The Answer does not, for example, present a reference that hepatocytes have receptors for IL-16 or evidence showing that IL-16 is known to play any role in liver function. Nor does the Answer show that CD4-PE binds IL-16 or, that if it does, that what the effect on the liver of decreasing the available amount of free IL-16 might be. In short, the Answer simply speculates that some possible interaction between CD4-PE and IL-16 could occur and hopes the Board will accept that speculation.

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argument.

It is, however, the Examiner's obligation in the first instance to present a *prima facie* case of obviousness. Applicants respectfully maintain that this obligation cannot be met by unsupported speculation and that the Answer fails to meet the Examiner's burden to set forth a proper *prima facie* case with respect to the obviousness rejection here.

Finally, Applicants observe again that the rationale advanced in the Answer was never presented during the more than 5 years of prosecution of the application. Under 37 C.F.R. §41.41(a)(2), the Applicants are prohibited from introducing any evidence to refute the Answer's new rationale. Conversely, since the new rationale has not been designated by the Answer as a new ground of rejection, the Applicants also do not have available to them the options afforded by §41.39(b). Since it is would be fundamentally unfair to permit an Examiner to introduce a new argument in the Examiner's Answer but not afford the Applicants a chance to submit any evidence that might be necessary to refute it, Applicants respectfully submit that the Board should reject the Answer's attempt to introduce this new rationale in the Answer.

(2). Contention that the Statements of the FitzGerald Declaration Are Limited to the Cells CD4-PE Immunotoxins Were "Intended" to Bind, Not the "Cells They Do Bind"

The Answer states "the declaration by Dr. FitzGerald was limited solely to what cells the immunotoxin were intended to bind not what they actually would bind. Consequently, Appellants statement that CD4-PE immunotoxins are analogous to anti-gp120-PE immunotoxins is misleading as CD4-PE immunotoxins will bind to other 'ligands' (i.e. all the natural ligands of CD4) whereas the anti-gp120-PE immunotoxins will only bind to cells expressing gp120." Answer, at pages 8-9, bridging paragraph. At page 14, the Answer emphasizes this contention even more strongly: "Dr. FitzGerald declared that the immunotoxins of the instant invention [are] analogous[] to the [CD4-PE and sCD4-PE immunotoxins] *in terms of the cells they were intended to bind* (not to what they actually bind). The declaration ignores the fact that the CD4-PE immunotoxins would necessarily bind to any natural CD4 ligand present." Answer, at page 14, emphasis in original.

Dr. FitzGerald's Declaration was introduced along with the Amendment dated October 13, 2006 ("October 2006 Amendment"), to respond to the Office Action dated April 13, 2006 (the "April 2006 Action"). In particular, it was written to respond to the contention in the April 2006 Action that CD4-PE immunotoxins were not analogous to the immunotoxins of the present invention because those of the invention would target cells expressing gp120 on their surface whereas CD4-PE immunotoxins would, according to the Action, purportedly bind any cell expressing CD4. See, October 2006 Amendment, at pages 12-13, bridging paragraph, *quoting* April 2006 Action. At paragraph 14 of his Declaration, Dr. FitzGerald corrected the April 2006 Action's fundamental misunderstanding of the science, stating that the Action's position was factually untrue, and that CD4 was a cell surface marker that does not bind to itself. FitzGerald Declaration, at ¶14. Dr. FitzGerald then continued by stating that "[w]hat the [CD4-PE immunotoxins] were intended to bind were cells infected by HIV-1, which express gp120 on their surface." FitzGerald Declaration, at ¶15. In other words, read in context, Dr. FitzGerald was stating that both immunotoxins were designed by their creators to bind to the same cells. Finally, Dr. FitzGerald concluded that paragraph by stating that both the CD4-PE immunotoxins and the immunotoxins of the present invention would "bind to cells expressing gp120, not to cells expressing CD4. I and others in the art would therefore consider them to be analogous in terms of the cells they were intended to bind." See, FitzGerald Declaration, at ¶ 15.

By taking Dr. FitzGerald's words out of context, the Answer attempts to give them a meaning they do not have. Dr. FitzGerald's statements were neither an equivocation as to the types of cells to which CD4-PE would bind nor an admission that CD4-PE would bind different cells than do the immunotoxins of the invention. Rather, read in context, they are a strong refutation of the fundamental scientific error underlying the position taken in the April 2006 Action.

(3). Contention that the results of the clinical trials would not have affected the motivation of the practitioner provided by the Matsushita and Bera references

The Answer further contends that the failure of the CD4-PE immunotoxins in clinical trials would not have affected the motivation of the skilled artisan allegedly created by the Matsushita and Bera references: "Moreover, it should be noted that the Matsushita and Bera references predate the publication of the CD4-PE clinical trials. Consequently, said results would have [no] effect on the thought processes (motivations) of the skilled artisan." Answer, page 7. The Answer further restates this contention in summing up its position. Answer, at page 16.

The Answer's focus on what the person of skill would have understood after the publication of Matsushita and Bera, but before the CD4-PE clinical trials, is a clear legal error. Under 35 U.S.C. § 103(a), obviousness is measured by whether the subject matter "would have been obvious to the person of ordinary skill in the art at the time the invention was made" (emphasis added). Under §103(a), therefore, the relevant inquiry is what the person of skill would have understood as of June 11, 1998, which is the filing date of the provisional application from which the present application claims priority. By 1998, the person of ordinary skill in the art had before him or her not only the Matsushita and Bera references, as relied on by the Answer, but also the results of the CD4-PE clinical trials. As Applicants showed in the Appeal Brief, at pages 7-10, the results of the clinical trials had a notably strong effect on the thought processes of the skilled artisan: the approach of using anti-HIV antibodies as targeting moieties for anti-HIV immunotoxins was abandoned. See, Appeal Brief, at pages 9-10, bridging paragraph.

Accordingly, the Answer's reliance on how the person of skill would have evaluated after Matsushita and Bera but before the CD4-PE clinical trials is a legal error. The correct inquiry is what the person of skill would have considered obvious in June 1998. And, as explained in the Appeal Brief, at pages 8-10, following the CD4-PE clinical trials, the art abandoned the uses of toxins targeted to Env proteins, including gp-120.

(4) Suggestion That Dr. FitzGerald May Have An Interest In The Case Because He Is An Employee Of "The" Assignee

At page 10, the Answer notes that the Appellants' declarant, Dr. FitzGerald, is an employee of "the" assignee and has coauthored numerous articles with the inventors. Answer, at page 10.[4]

It is true that Dr. FitzGerald is an employee of the United States Government, one of the assignees of the subject application. His status as a Federal employee is set forth on the face of both his Declaration and c.v. (see, Appeal Brief Evidence Appendix, Part II, Exhibits E and E1). It is also true that many of Dr. FitzGerald's almost 200 scientific publications have been authored with those of the inventors, including Dr. Pastan, who are also Federal employees, and that, as stated in the c.v., he is a section chief in the Laboratory of Molecular Biology, which is headed by Dr. Pastan.

By pointing out Dr. FitzGerald's employment by "the assignee" and his publications with the inventors, the Answer presumably intends to imply that Dr. FitzGerald has some interest in the outcome and that his opinion should therefore be discounted. The Answer does not show, however, that Dr. FitzGerald's status or pay as a 26-year Federal employee would be affected in any way by the opinions set forth in his Declaration. Further, that many of his almost 200 scientific publications on the subject of immunotoxins have been co-authored with one or more of the inventors is not surprising; Dr. FitzGerald and his colleagues are among the most expert in the world on immunotoxins, as reflected by the numerous publications in this area set forth in his c.v. In short, the Answer fails to show that Dr. FitzGerald has any personal interest in the outcome of the present case.

In addition, Dr. FitzGerald's Declaration contains a number of factual statements. Dr. FitzGerald's opinion statements are in turn supported by the factual statements. MPEP §716.01(b) states that the probative value of an expert opinion may be assessed by considering (i) the nature of the matter to be established, (ii) the strength of any opposing evidence, (iii) the

[4] The subject application has two assignees: the Government of the United States and The Scripps Research Institute.

interest of the expert in the outcome of the case, and (iv) the presence or absence of factual support for the expert's opinion. Under MPEP §716.01(b), the interest of an expert in the outcome, even if the expert can be presumed to have one, is also only one of the factors to be considered by the Examiner. The Examiner is also supposed to consider, for example, the factual support for the opinion. While the Answer attempts to discount the Declaration by implying that Dr. FitzGerald might have an interest in the outcome, the Answer focuses on this implied interest without also performing an assessment of any of the other factors set forth in § 716.01(b). There is, for example, no evidence that the Answer also performed the required assessment of the factual support provided in the Declaration.

In short, the Answer fails to show that Dr. FitzGerald has any interest in the subject matter or that the opinions expressed in his Declaration are unfounded. Further, the Answer fails to show that any of the factual statements in the Declaration are erroneous. The Board is respectfully requested to ignore the Answer's unsupported attempt to discount the Declaration and to give full weight and consideration to its statements.

(5.) Contention That the References Cited by the Appellant Do Not Objectively Represent the State of The Art

The Answer dismisses the import of two references cited by the Appellants, a "Perspective" published in the Proceedings of the National Academy of Sciences, Berger, Moss and Pastan, Proc Natl Acad Sci 95:1151-11513 (1998) (hereafter, "Berger", Evidence Appendix, Part II, Exhibit D) and Goldstein et al., J. Infect Dis 181:921-926 (2000) (hereafter, "Goldstein", Evidence Appendix, Part II, Exhibit E), on the grounds that they "were coauthored by members of the inventive entity and hence are not deemed to [be] representative of the views of the art as a whole or even an objective third party." Answer, at page 10.

It is true that the third named author of the Berger reference is Dr. Pastan, an inventor of the subject application. It is also true that the first and second authors, Drs. Berger and Moss, are employees of the National Institute on Allergy and Infectious Diseases, or "NIAID", the Government's lead agency for combating HIV and Dr. Moss is, like Dr. Pastan, a

chief of an NIH laboratory and a member of the National Academy of Sciences. See, Appeal Brief, at page 15. Dr. Pastan is in the National Cancer Institute.

The Answer provides no basis on which the Board could reasonably conclude that Dr. Pastan could cause these other eminent scientists from a different NIH institute, and the one directly concerned with combating HIV, to put their names and reputations on a Perspective on HIV treatment in the Proceedings of the National Academy of Sciences if they did not believe it to be truthful and accurate. Moreover, the Perspective was edited by Dr. Anthony Fauci, the Director of the NIAID, and himself a member of the National Academy of Sciences. See, Appeal Brief, at page 15. Once again, it is not credible that Dr. Fauci would put his name and reputation on a paper in PNAS on a new approach to HIV treatment simply because of the presence of a lab chief from a different NIH institute.

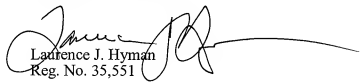
Similarly, the first and second authors of the Goldstein reference are from the Albert Einstein College of Medicine and the senior author is the Edward Berger who is the first author of the Perspective discussed above. See, Appeal Brief, Evidence Appendix, Part II Exhibit D. Once again, the Answer provides no evidence that there would be any reason why three other scientists, from two institutions other than the one employing Drs. Pastan and Bera, would put their names and reputation on a paper in the open scientific literature in which they did not believe.

In short, the Answer's attempt to discredit the Goldstein and Berger references is another indication of the Answer's stubborn insistence on discounting any evidence contrary to the thesis of its rejection. The Answer provides no evidence that suggests that these publications in the open scientific literature, authored by persons not associated with the subject application, should not be given weight and consideration. The Board should give full weight and credit to the references as fairly reflecting the understanding of the art at the time of the invention.

CONCLUSION

For all these reasons, it is respectfully submitted that the rejections of the claims should be reversed.

Respectfully submitted,



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